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MEDICAL STAFF CONFERENCE

Malaria

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* *Malaria is a disease of worldwide importance, but one which we infrequently encounter here. Dr. Robert Dreisin will present the case of a patient who was treated here.*

DR. DREISIN:† The patient is a 21-year-old Nicaraguan woman who was presented to us with a history of two weeks of chills and fever. She was apparently well when she left Nicaragua for the United States four months before admission. Two weeks before admission she noted a mild chill with fever, which lasted about four hours, then faded. It occurred the next day and approximately two days thereafter. The attacks were of increasing severity and she noted scleral icterus and darkening of her urine with the attacks. By the time she was presented to us in the Emergency Room she had been treated by a wide variety of physicians with a wide variety of antibiotics. On physical examination the patient was in no acute distress and was afebrile. Mild scleral icterus and a hemic cardiac flow murmur were present, but results of the physical examination were otherwise unremarkable. There was no hepatosplenomegaly. Admission hematocrit on the blood smear revealed many Plasmodium vivax ring forms (trophozoites) and larger red blood cells, with schizonts present. There were some merozoites but no gametocytes on the smear. The patient was treated with chloroquine and she remained afebrile and asymptomatic thereafter.

DR. SMITH: *She has been seen in the clinic for subsequent followups and is doing well. She is not actually here for presentation this morning. Our discussant will be Dr. Donald Heyneman, Professor of Parasitology in the Department of International Health.*

DR. HEYNEMAN:* The present case is very typical of uncomplicated vivax malaria. The patient is one of about 200 million persons who suffer from malaria annually, that is equal to about 12 percent of the 1.7 billion humans—half the world's population—who occupy various tropical and subtropical regions of the world that are or recently were endemic for malaria. About 650 million people, 38 percent of the exposed population, are now considered freed of malaria and another 710 mil-

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lion are partially protected or freed of endemic (but not of periodic) malaria. Yet there are still 380 million more, chiefly in tropical Africa and the Amazon basin, where no malaria control has begun.[1] It has been roughly estimated that about half of these unprotected people are infected. Concern in this country has been greatly heightened by the reappearance of imported malaria in the United States, chiefly from returning Vietnam veterans—4,000 cases in 1970, 3,000 in 1971. The whole question of malaria is now in a confused state due to importation and reappearance of malaria in areas in which it was thought to be controlled (or even eradicated), the development of widespread resistance to insecticides by the mosquito vectors, and in Southeast Asia and South America the resistance of the most dangerous plasmodial agent to drugs.

There have also been political or administrative interference and financial slowdowns of many malaria eradication campaigns, leading to loss of the World Health Organization (WHO) thrust and of public confidence in the possibility of worldwide malaria eradication, a basic WHO goal since 1955. This campaign is one in which the entire United Nations is very deeply involved. Political repercussions of failure of such a program, the most ambitious and costly public health campaign ever attempted, are self-evident. Nonetheless, reappraisal and reorientation toward malaria control rather than eradication is under way. The philosophic and practical differences between these two approaches are basic ones and must be fully appreciated for both their economic and epidemiological significance.

Epidemiology and Host Response

In our own smaller sphere, we have to advise and protect thousands of American tourists who in increasing numbers are going to Africa to visit game parks and who for the most part receive from their travel agencies no information on malaria prevention. Cases that appear among these highly vulnerable, nonimmune persons tend to be very severe, with a fatality rate of 10 percent among the patients with Plasmodium falciparum (malignant tertian) malaria.[2] Occasionally, we read of a returning veteran who suffers a suddenly fatal cerebral involvement from undiscovered (or "cured") falciparum malaria—a disease of the utmost danger (50 percent fatality rate), which demands instant life-saving therapy. We read, too, of new dangers to whole blood recipients[3] and of malaria transmission from shared narcotic addicts' needles.[4] Cases of imported malaria in the United States are summarized in a recent Center for Disease Control (CDC) surveillance report;[5] more general aspects of the problem have also recently been reviewed.[6]

In order to evaluate these problems and help you to assume your clinical responsibilities, I would like first to separate in your minds two distinctive patterns of host response to the same infectious agents. The first of these leads to endemic (or stable) malaria. This condition exists in an indigenous population that is repeatedly exposed to malaria from birth, with continuous high level of infection, but low manifest illness in the adult population. Those children who are exposed to malaria infection through infancy (and are among the survivors), are by the age of five years essentially immune to that strain of Plasmodium. Some investigators believe this degree of immunity is not possible among persons first exposed after the age of five years (which may include the patient presented here).[7] The suppressed manifestation of malaria among these "immune" persons may actually be passively acquired protection from mother's milk, followed by a resistance induced by a low-level prevailing infection ("premunition"). To treat such persons who are not severely ill could cost them their acquired protection. They then must return to their malarious homeland at considerable peril. Various degrees of endemic malaria have been described, based on the percentage of two- to nine-year-olds showing splenomegaly: Holoendemic (+75 percent), hyperendemic (50 to 75 percent), mesoendemic (11 to 50 percent) and hypoendemic (less than 11 percent).

Hypoendemic malaria is a characteristic of the second epidemiological pattern or host response to which I referred. It is typified by severe outbreaks, hence is called unstable, periodic, or epidemic malaria, and occurs in regions sporadically or periodically exposed, chiefly striking large numbers of nonimmune children. Occasionally, environmental or epidemiological conditions permit malaria to sweep over a region that generally has a very low level of infection, often with extreme virulence and, in the case of falciparum malaria, a very high death rate. This may be due to an unexpected increase in the population of the vec-

tor mosquito resulting from favorable breeding conditions, the sudden introduction of a better vector, human migrants carrying a different strain, or perhaps the mutation of the local strain to a more virulent disease agent. It also occurs when malaria is accidentally reintroduced in a region from which the disease had been eradicated, since eradication campaigns are designed only to interrupt transmission by infected mosquitoes and not to destroy the entire Anopheles population.

Whether a local upsurge of cases results from altered epidemiological conditions or from imported malaria, a highly vulnerable nonimmune host population will be affected, and this population consists mainly of the children born after the last epidemic or since local cessation of transmission. The resulting disease is what we call typical malaria. It is the only form most American clinicians see, though in fact it represents only a fraction of the existing cases. It is what we treat in an American soldier from Southeast Asia, a Peace Corps volunteer from South America, or a tourist returning from Africa. All display the host reactions of a nonimmune person—the classic or textbook syndrome of 48- or 72-hour fever and chills. The far more common suppressed infection (as opposed to disease) is seen in this country only in an occasional visitor or student from Africa. A comparable condition may be seen in a patient partially protected by chemosuppressant drugs. It also may be identified from tracing the sudden death from malaria of a blood transfusion patient to a "cured" or nonsuspected donor, one who subsequently (and often with difficulty) is proved to be infected.

Proper handling of a malaria patient, therefore, rests on careful determination of his history as well as precise identification of the disease agent. You must obtain and evaluate a thorough history of your patient's way of life—his place of origin and subsequent travels, the frequency and duration of his past exposures, and the probability of his returning to the same area. To this must be added genetic characteristics of your patient, as Blacks tend to be more malaria resistant than are Whites, and African Blacks are more so than American Blacks. The sickle cell trait and other hemoglobinopathies and glucose-6-phosphate dehydrogenase (G6PD) deficiency appear to be important factors in the pattern of natural selection for malaria resistance that continually occurs in highly endemic areas.

In holoendemic or hyperendemic regions—most of tropical Africa, Central America and tropical South America (except Venezuela), parts of Southeast Asia and Polynesia, much of southern India—malaria is one of the basic conditions that is part of and helps determine the way of life of the people. After childhood, the residents rarely suffer typical cyclic malarial fevers. Yet most of these populations are chronically infected, with plasmodia in the liver and only for brief periods in the bloodstream (presumably the bloodstream forms are cleared by antibody action and activated phagocytes).

It is not possible to tell whether this is a true immune response, an infection-immunity or premunition resulting in a chronic suppressed infection, or a condition induced by repeated reinfection. It does appear to represent a host-parasite balance marked by high gammaglobulinemia and splenomegaly in the human, and a low-level but viable infection capable of being transmitted to other biting anopheline vectors. Nonetheless, it is costly. The infected child, especially, is victimized. He suffers repeated energy-sapping bouts of fever and chronic anemia with a need for food energy to replace loss from fevers and for continual iron and protein replacement, occurring usually during the most critical first three years of life. This is particularly true if the maternal milk-protection is not sufficient, as is usually the case in malnourished populations. Frequently these losses are compounded by bloodsucking hookworms and other energy-demanding parasites. When malnourished infants suffer attacks of falciparum malaria, the eventual effect is a serious inroad on growth and mental development, with diffuse hepatic fibrosis and hepatomegaly.[8]

This is a yoke of quiet suffering seen throughout the tropics and subtropics. Evidence of illness is greatly reduced among adolescents, though healthy-looking children with falciparum malaria frequently have a heavy load of parasites in their blood. Adults in these highly infected regions, whether immune to or tolerant of their constant plasmodial guests, are not measurably ill, though some may have a greatly enlarged spleen and possibly hepatomegaly as well. On the other hand, should they move into a different falciparum malaria region, they may contract a quite heavy new infection, though this appears not to be the case with the other species of Plasmodium.[8]

In hyperendemic falciparum areas we appear

to be dealing with human hosts who have built up resistance against a specific strain of this species and are protected by genetic factors, by some degree of acquired residual immunity to the local falciparum strain, and by a further degree of protection induced by premunition. Resistance against the other forms of malaria (vivax, malariae, ovale) is comparable, but these species of Plasmodium show less tendency to form a number of immunologically distinct local strains, so resistance is less geographically restricted.[8]

Despite the high degree of human adaptation to malaria, disease reactivation may be induced by stress, protein deficiency, age, concurrent infection, or a change of residence location (the latter in the case of falciparum malaria). Nonetheless, the pattern of tolerance that has evolved has enabled millions of persons to survive repeated infection with malaria (and a variety of other parasites), all competing for inadequate protein and food energy reserves. The so-called laziness of tropical living is more often than not this restriction of energy reserves, part of the adaptation to malaria. Despite vast expenditures and an unparalleled international effort, malaria remains the number one disease of mankind.

Control vs. Eradication

Retreat from the unduly optimistic WHO vision of world malaria eradication means that we now must face the prospect of developing a permanent (hence ultimately more costly) control program. This depends upon the reduction of malaria transmission to a tolerable level as a permanent obligation, one that does not involve the huge and often fruitless labor of removing the last vestige of infection within a prescribed period, usually seven to ten years. Many factors have combined to make that last 10 percent harder to achieve (and maintain) than the first 90 percent of malaria reduction. The problem is not caused simply by the rapidly growing populations of insecticide-resistant mosquitoes, by chloroquine-resistant Plasmodium falciparum, by movements of nonimmune or infected human populations from and into cleared areas, or by the difficulty in organizing, training, and supporting the mosquito spray teams in remote undeveloped tropical regions. Fundamentally, our failure to achieve eradication is a reflection of our failure to appreciate the range and diversity of ecological interactions in the epidemiological complex involved in malaria transmission.

The greatly increased selection pressure favoring drug-resistant strains of Plasmodium and DDT-resistant strains of Anopheles are expressions of the genetic flexibility of these organisms, just as is the human genetic response that has favored selection of malaria resistance or tolerance through selection of heterozygotes for sicklemia,, HbC, HbE, thalassemia, or of G6PD deficiency. But to this genetic adaptability of parasite, vector, and human host, we must add the enormous range of habits and species of Anopheles mosquito vectors involved—some 30 species in Malaya alone, perhaps 100 or so worldwide. Each vector species (or strain in many cases) has its own highly characteristic biting habits and food preferences, its own breeding locations and its own population dynamics with competing species, predators, and parasites. Often we spray for one mosquito only to find that another soon replaces it, perhaps with habits protecting it from DDT. An example is the replacement of an easily killed vector with a species or strain that does not land on household walls where spraying is concentrated. Just as we are discovering many unexpected repercussions of wide-scale application of DDT in agriculture, we are beginning to appreciate the variety of ways in which the epidemiological pattern of malaria transmission is expressed in different geographic areas and eco-systems. Therefore, a single pattern of control, based on a familiar transmission cycle, simply cannot be applied worldwide and expected to succeed.

Yet the feasibility of worldwide malaria eradication is based on the premise that a universal epidemiology, with only minor variations, is the general one: Infected (or susceptible) mosquitoes fly into a house, feed, rest on a wall or on furnishings and then fly off to rest, refeed at intervals (which permits development of the ingested sexual stages to infective sporozoites and their transmission), and finally lay eggs to complete their life cycle. So, one need only spray the house, inside and out, and the mosquito will land on it (before or after feeding), and then fly off to die. This method controls precisely those mosquitoes in the act of becoming infected or transmitting the agent. Maintain the residual insecticide, treat *all* infected humans, and local active transmission will be blocked, resulting in a dramatic drop-off of new cases. Continue this for several years, actively search for and treat all cases, and within five to seven years, all transmission will have been stopped and the Plasmodium (not the mosquito) will have been locally eradicated. Do this on a well-coordinated and

properly-funded national and international scale, and malaria will become a thing of the past.

In many areas this scheme has worked remarkably well. Malaria is essentially eradicated from the Mediterranean basin, its classic nidus. But in Malaya, for example, replacement vectors bite man outside of his home from inaccessible forest breeding sites. Elsewhere, mosquitoes bite inside houses but without lighting on the wall before or after feeding. Or they may bite only in forest sites. By a change of habits or replacement by other vectors or by other means, the vectors may circumvent our notion of where and how every self-respecting, proper Anopheles female *ought* to inoculate its human host with plasmodial sporozoites. We find that not only has resistance to DDT (and to nearly every other insecticide as well) been favored by natural selection in continuously sprayed areas, but also inherited behavioral patterns have been subject to natural selection, permitting survival of mutant forms or of different species possessing the favored traits.

The view that nature abhors a vacuum is correct. Eradicate one species, another will promptly replace it—and we seldom can predict which one. Nature is not only incredibly rich and varied, but enormously variable and adaptable as well. The small proportion of mosquitoes that escape the DDT assault can and, at a rapidly accelerating rate, will replace those that were eliminated. Complexity and adaptability is the "normal" pattern in nature, whereas our view is necessarily narrowed to specific human objectives reached by carefully prescribed methods along clearly marked and economically supportable pathways.

The assumption that what works some of the time must therefore work all the time against malaria has proved to be a catastrophic error in judgment, one that has involved vast effort and expenditure, and is now reaping increased disappointment and disillusionment. Hence the new efforts by WHO malariologists and others to make their attacks as adaptable as is their target. Control of malaria, as opposed to eradication, suggests survival within a balance, working within the system rather than attempting to destroy it Don Quixote-style in order to substitute our own system. We may yet discover that the same principle of parasite suppression rather than elimination applies to many other (but obviously not all) human infections as well. Controlled, low-level infections that permit development of tolerance, adaptability, premunition, or immunity may be preferable to total removal of every last infective agent. Our highly sanitized society with its hypersensitivity to any agent found dwelling within us is a reflection of the hothouse culture in which we live. We are obsessed with the need to obliterate any semblance of dirt, germs, microbes, worms, or vermin—terms that suggest roles we have defined for them and allocated as being in accord with *our* conception of life rather than theirs.

Lest this lead too far afield, I should like to return briefly to malaria and its presence, not in populations, but in *people*—your individual patients. If you were to treat an infected African who was living here for a short period, you should approach his case differently than you would that of an African who is here to stay. An American returning from Africa with falciparum malaria requires alert treatment oriented to the dangers that he faces in his nonimmune state. Not only does your patient require your keen attention—so does the health of others affected by him. In 1953, a Marine returnee from Korea spent a few nights camping ten miles from a Camp Fire Girls' outing. That night he was heavily bitten by locally abundant mosquitoes. It happened that these were Anopheles freeborni, a splendid malaria vector. (In 1833, this species was responsible for a wild epidemic that wiped out most of the Indians in the Central Valley of California; later, malaria was a scourge of the gold mining camps; about the turn of the century it was associated with irrigation in the Central Valley and made California the "most malarious state in the Union" with over 5,000 cases annually).[9] The slumbering Marine packed up the next day and went home; but before the summer was out, 35 girls from the nearby camp came down with vivax malaria, which fortunately did not remain as a viable focus of infection in the area.

Epidemiological insight with recognition of your patients' special requirements are part of the message imparted with the case of the patient presented here today. But this insight can only follow from your recognition that the problem exists or that it could exist in your practice. Without this mental preparation and anticipation, malaria will pass you by as it has nearly every physician who has initially treated with penicillin (for "flu") the malaria patients subsequently sent to CDC or to

major medical centers. The patient whose case was presented here is, unfortunately, a typical example. In an Army hospital, such misdiagnosis is rare, due to the physicians' expectations. Any patient seen by you who has been to an endemic malarious area within the previous five years (sometimes longer) should cause you to see over his head a red-flashing warning light blinking out the message: *malaria*. Recrudescent cases may develop two or more years after a Vietnam veteran's return, especially with vivax (benign tertian) or malariae (quartan) malaria. Even falciparum (malignant tertian) malaria, which is unique in that it does not continue to reproduce in the liver and thereby "reseed" periodic blood relapses, still may survive in infected liver parenchymal cells in an apparently suppressed state for 18 months (or longer in a few cases) before it breaks out into the bloodstream. It may, after such a delay, also appear in its pernicious and rapidly fatal form in the capillaries of brain, kidney, lungs, or intestine.

Pathology

Although all forms of malaria are uncomfortable and often temporarily disabling when a paroxysm strikes a nonimmune person, only Plasmodium falciparum, the agent of malignant tertian malaria, is life-threatening. Rarely, very young, severely malnourished children infected with P. vivax, P. malaria, or P. ovale may die of the malarial infection (or a combination of insults) or have severe anemia. More typical in these children is an insidious course of continuing relapse and reinfection with splenomegaly and chronic ill health. Among well nourished persons the sequence of relapses or reinfections is generally followed after about six months by an acquired immunity, or a state of premunition from successive exposures, or a combination of these. Despite much study of the subject, we can only say that resistance does develop, but the precise cause is still disputed.

Immunity is only effective against the blood forms, the merozoites released in cyclic waves that induce the 48-hour (tertian) or 72-hour (quartan) fevers. However, the liver stages (exoerythrocytic phase) are safe from the host's immune response. Hence, relapse originating from the liver hideout may occur over a prolonged period provided that the blood-based immune response has waned enough to allow a recrudescence of the erythrocytic schizogony. In cases of P. malariae the infection is particularly long-lived. The patient may show no sign of malaria for 25 years or more and then have a relapse, presumably from a reduction in the blood-based immunity. P. vivax relapse can occur seven years after the last exposure, somewhat less for P. ovale. These three species, the less pathogenic ones, can sustain the infection because of continuous merozoite multiplication in the liver, a secondary tissue schizogony that follows the initial growth of the parasite from sporozoites inoculated by an infected mosquito.

However, P. falciparum can undergo only a primary tissue schizogony. Sporozoites inoculated by the mosquito enter the liver parenchyma cells within an hour or two and undergo just two cycles of schizogony, rather than a continuous secondary series. Hence, it can be called the kill-or-cure malaria: once the illness is passed—and cured—it won't recur. However, a repressed infection from partially successful drug therapy or partial resistance to chemo-suppression may erupt a year or more afterwards. These are the "recrudescent" falciparum cases found among supposedly healthy or cured Vietnam veterans.

It is well that no true secondary liver schizogony occurs in falciparum malaria. The primary one is bad enough and is responsible for nearly all of the deaths and most of the severe sequelae—the "pernicious" form. This effect is caused by a peculiarity of the growing parasite within the red cell. The trophozoite's development modifies the nature of the host red cell wall, causing the infected cells to become sticky. The sticky cells tend to clump in capillary beds of internal organs (hence these stages are rarely seen in peripheral blood). Circulatory restriction, stasis or hemorrhage and necrosis of the affected area follow and produce a pernicious anemia. The clumped red cells tend to adhere to the endothelium of small capillaries, particularly where the capillaries suddenly narrow, as in the intestinal villi, kidney glomeruli, lung alveolar walls, and, of greatest threat, in the cerebral capillaries. The thrombosis is followed by leakage, local anoxia and necrosis causing nearly all of the characteristics of the malignant anemia including intestinal hemorrhage and mucosal sloughing, cardiac infarcts, kidney malfunction, jaundice and algid or other forms of cerebral malaria.

One additional form of falciparum malaria rarely encountered today, blackwater fever, is less well understood. It is a rapidly fatal hemolysis related to inadequate quinine treatment of falciparum malaria. Administering the drug to sensitized

persons may precipitate an often-fatal hemoglobinuria. Apparently the parasitized-quininized red cell acts as an antigen against which hemolysins form. Then a new attack of malaria, treated with quinine, provokes a crisis, causing intravascular hemolysis, renal tubular damage, renal cortical ischaemia, renal failure, profound anemia, and jaundice.[8] But since malaria therapy with quinine is rarely attempted, (see below) this man-made disease is largely historical.

Another malaria antigen-antibody complex associated with nephropathy does occur, however. This is the nephrotic syndrome or "quartan nephrosis" associated with cases of P. malariae in children and characterized by generalized edema and albuminuria at the early stages. It has been suggested that the parasite sensitizes the kidney and an auto-antigen is produced, with the antigen-antibody complex showing an affinity for the g'omerular basement membrane. Other observers have concluded that the tubular damage is degenerative and not inflammatory, causing nephrosis instead of a nephritis.[8] Early treatment will prevent the later irreversible changes and bring about a prompt cure.

Blood destruction leading to anemia is also far more severe with falciparum than with the other malarias. This is related to the type and number of red blood cells invaded during the erythrocytic stage. In falciparum malaria, 200,000 or more cells per cubic millimeter of blood may be destroyed. All ages and types of red cells are invaded. Overwhelming infections of 50 percent of the red cells may occur—though infections at half that level are usually fatal.[10] Vivax malaria tends to focus on younger red cells and seldom exceeds 35,000 cells per cu mm; malariae, the least destructive (except for the nephrotic syndrome), usually affects older erythrocytes, 5,000 to 15,000 per cu mm.

Treatment

Most cases of uncomplicated malaria will respond readily to 4-aminoquinoline therapy—chloroquine phosphate, 2.5 grams (1.5 gram base) over three days; and recurrence of vivax, malariae, or ovale malaria generally can be prevented by using the tissue-active drug primaquine phosphate (26.3 mg, 15 mg base) daily for two to four weeks. This is a secondary tissue schizonticide, the only one that can produce a "radical cure" for the recurrent forms. The latter drug should not be used in G6PD deficient persons (a trait more commonly found in Blacks than Whites in the United States) as it may induce severe, though temporary, hemolytic anemia.

If your patient is to spend a limited time in an endemic area where resistant falciparum is not a problem, chemo-suppression with chloroquine (500 mg once weekly) is essential, starting two weeks before and continuing *eight weeks after* leaving the endemic area. The Army weekly chemophrophylactic pill (chloroquine, 0.3 gram base, plus primaquine, 0.045 gram base) may be taken if the patient is not G6PD deficient. However, preventive therapy with primaquine can just as well be prescribed after his return (15 mg base daily for two weeks or for four weeks if the area is a focus of resistant malaria).

If your patient is heading for parts of South America or Southeast Asia where chloroquine-resistant falciparum strains are well established, "only the sulfones and sulfonamides are available to us at the present time as reasonably assured suppressives of multi-drug-resistant-P. falciparum," (reference 11, pp 739-40; *cf* also 12 for a broader review of resistance). The most widely used oral sulfone is dapsone (DDS). Another, diacetyl-DDS (DADDS), is given intramuscularly at intervals of several months. Chemo-suppression with DDS (25 mg) has been used either daily with chloroguanide or at weekly intervals with pyrimethamine or chloroquine plus primaquine.[7] Another oral combination, sulfadoxine (sulfomethoxine) 500 mg, with pyrimethamine 25 mg (adult dose), given at weekly intervals, has protected nonimmune persons in a highly drug-resistant area of Laos.[11] Fear over development of resistance among pathogenic bacteria caused by extensive use of sulfonamides for malaria prophylaxis has been a deterrent to wide-scale field testing of these drugs.

Curative treatment of chloroquine-resistant falciparum malaria among nonimmune persons who have access to supervised treatment requires a 14-day quinine regimen. Three treatment schedules have recently been described (reference 11, p 741) using quinine sulfate, 2 grams daily for 14 days, alone or with pyrimethamine and/or various sulfa or sulphone compounds. Most critical is the immediate life-saving treatment of pernicious malaria with cerebral involvement. Cerebral involvement is indicated by falciparum infection with various central nervous system manifestations: Deepening coma (if entire cortex is involved); hemiplegia or Jacksonian epilepsy (motor area);

algid malaria (pituitary and adrenal involvement); hyperpyrexia (to 42°C)—involving thermo-regulatory centers in the pons; bulbar paralysis (hind brain); tremors (basal ganglia), etc.—depending upon the region of the brain affected.[8] Treatment for this and other forms of pernicious malaria (responsible for capillary thrombi or stasis, leading to hemorrhage from leaking vessels, tissue anoxia and necrosis) should be intravenous quinine dihydrochloride (0.6 gram in 300 ml saline solution over at least 30 minutes every eight hours for a maximum of three doses). Catchpool[7] suggests preceding the intravenous quinine with a glucocorticosteroid (dexamethasone, 4 to 6 mg every four to six hours). Similar emergency measures are required for pernicious malaria of the intestinal tract, leading to hemorrhage into the lumen, mucosal sloughing, and rapidly fatal dysentery. Endothelial involvement of cardiac tissue and renal glomerulonephritis are other forms of rapidly fatal pernicious falciparum malaria.

Prevention and treatment of drug-resistant malaria are limited and imperfect; and they are under intensive and often frustrating research, involving a number of drugs in a variety of combinations. New procedures are developed and tested, only to be compromised or blocked by new forms of resistance or untoward drug reactions. Clearly we need new and more effective antimalarials—a very different view from those blissful ones held ten years ago. Malaria specialists in those days were apt to complain that we would be hard-pressed to find good examples of malaria for study and that we would never again be able to wrestle with the fascinating problems associated with intracellular malaria parasites. It reminds one of the early stages of the DDT-honeymoon, when houseflies, it was thought, soon would be relegated to pins in museum trays. That was in the days before the advent of the 1973-model Superfly. Present-day mosquitos suggest a similar future, as do the strains of Plasmodium they transmit. These evolutionary changes in our own lifetimes reemphasize a lesson we seem destined to re-learn continually: Living things do not serve man alone, nor do they follow the laws or read the textbooks we write about them. Instead, they form continuously changing, adapting, interacting, and interdependent communities that are oblivious to our special needs or wishes.

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